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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/540,024	03/31/2000	Arthur O. Tzianabos	B0801.7169	1627

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Helen C. Lockhart
Wolf Greenfield & Sacks PC
600 Atlantic Avenue
Boston, MA 02210

EXAMINER
LIU, SAMUEL W

ART UNIT	PAPER NUMBER
1653	

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Please find below and or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/540,024	TZIANABOS ET AL.	
	Examiner	Art Unit	
	Samuel Wei Liu	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19,37,61,63,65,67,101,103,104,106,108,111,127,138 and 147-163* is/are pending in the application.

4a) Of the above claim(s) *37,61,63,65,67,101,103,104,106,108,111,127&138* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19 and 147-163* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The drawing filed 4 November 2002 have been approved by US PTO drafting. Applicant reinstates original claims 20-36 in the response filed 20 November 2002. It appears that claims 20-36 were canceled (preliminary amendment filed 18 September 2000). Claims 20-36 in the amendment filed 4 November 2002 are entered as new claims 147-163 (37 C.F.R. 1.126), respectively, which are drawn to elected invention, Group I. Note that When claims are added, they must be numbered by the applicant consecutively beginning with the number next following the highest numbered claim previously presented (whether entered or not) (see 37 CFR 1.126). Also, preliminary amendment filed 18 September 2000 as to cancellation of claims 20-36, 38-60, 62, 64, 66, 68-100, 102, 105, 107, 109-110, 112-126, 128-137 and 139-146, and Applicant's request for one-month extension of the time filed 4 November 2002 have been entered. Therefore, claims 1-19, 37, 61, 63, 65, 67, 101, 103-104, 106, 108, 111, 127, 138 and 147-163 are pending; claims 37, 61, 63, 65, 67, 101, 103-104, 106, 108, 111, 127 and 138 are withdrawn from further consideration by the examiner, as being drawn to a non-elected invention. Claims 1-19 and 147-163 are pending and reexamined in this Office action.

Grounds of objection and/or rejection not explicitly restated and/or set forth below are withdrawn.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-19 and 147-153 and 155-163 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 19 are unclear as to whether or not repeating charge motifs are or are not the "repeating units" in view of dependent claims. Of note is that applicants discuss this issue of repeating unit(s) and charge motif but does not clarify the issue in the claim(s).

Claim 2 is unclear as to whether or the non-repeating units refer to the "repeating charge motifs" as compared to the intervening sequence or whether or not the "non-repeating" units refer to different amino acid residues in a particular sequence.

Claim 3 does not further define how the repeating units are differently placed or how they differ in number compared to claim 1.

Claim 4 is unclear as to "identical repeating units" because as written in claims 1 and 4, there can be the "two repeating charge motifs" which is repeated (repeated here can be interpreted as an identical repeat).

Claims 3-4 and 148-149 are indefinite as to whether or not the recited repeating unit is same as the repeating unit set forth in claims 1 and 19, respectively. Given the repeating unit differs from that set forth in claims 1 and 19, whether or not the claimed repeating unit has structural limitations set forth ion claims 1 and 19, *e.g.*, containing charge moieties. If the repeating unit refers to the repeating *charge* motifs, this does not further limit the claims.

Claim 5 is indefinite as what is a non-identical repeating unit as non-identical would suggest the units are not the same and, if not the same, they are not repeats.

Claim 6 recites "mixed polymer"; the recitation renders the claim indefinite as only one polymer is recited in claim 1. What other polymer is present or is the claim means? Is mixed to

mean a peptide-nucleic acid polymer as recited in claim 7? This is not found in claim 6 nor in claim 1.

Claim 15 is unclear as to how native would differ from the claim recitation of non-native.

In view of the foregoing discussion, claims 147-163 are also indefinite.

Response to the rejection under 35 USC 112, the second paragraph

The response file 4 November 2002 has been considered but is unpersuasive. The reasons why applicant's comments are unpersuasive are addressed in the above stated ground of rejection under this section of the statement.

Claim Rejections - 35 USC §102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The claims 1-6, 14-16, 18-19, 147-148, 152-160 and 162-163 are rejected under 35 U.S.C. 102(b) as being anticipated by Ferrari, F. A. *et al.* (US Pat. No. 5514581, newly cited).

Ferrari *et al.* disclose a polymer (SEQ ID NO: 102, columns 127-128) that is less than 50 KDa and comprises two repeating motifs, each of which contains a positively charged and a negatively charged moiety (**Arg**-Gly-**Asp**) wherein the two repeating units are separated by a neutral sequence having a distance larger than 32 Å (in view of that a dimension occupied by 8

amino acid residues is equivalent to 32 Å). The above Ferrari's disclosure teaches the all the limitations in regard to the polymer set forth in claim 1.

Claim 1 recites "a pharmaceutical composition"; note that the recitation of "pharmaceutical" has no patentable weight *per se*, absent factual indicia to the contrary; thus, the Ferrari's patent is applicable to the claim 1 disclosure. The Ferrari's patent teaches the subject composition for interacting with solution (see column 2, line 34) or combined with organic material (see column 48, line 10) which meets the limitation "pharmaceutical carrier" in the claim. Thus, Ferrari's teaching anticipates claims 1, 19 and 163 of the current application. Since the repeating unit is identical, Ferrari's patent also anticipates the application claims 3, 4 and 148. Because the repeating unit Arg-Gly-Asp has positive to negative charge ratio of 1:1, the Ferrari's patent is also applied to the application claims 18 and 162.

Ferrari *et al.* teach a polymer (SEQ ID NO: 111, columns 133-134) comprising non-repeating units wherein contain a positively and a negatively charged residues (see **Lys**-Gly-Ala-**Asp**, and **Arg**-Gly-**Asp**), as applied to claims 2, 5 and 147 of the instant application.

Ferrari *et al.* teach a composition produced by crosslinking the polymer with other type of polymer or materials, as applied to claims 6, 16 and 160 of the instant application.

Ferrari, *et al.* teach the polymer that is recombinantly synthesized (see abstract), as applied to the application claims 14-15 and 158-159.

Ferrari *et al.* disclose (i) a polymer (SEQ ID NO: 66, columns 101-104) that is less than 50 KDa and comprises five repeating motifs, each of which contains positively charged and negatively charged moieties, *e.g.*, the repeating unit I (**Lys**-Gly-**Asp**) and unit II (**Arg**-Gly-**Asp**)

wherein the two repeating units I and II are contiguous, as applied to the application claim 154; (ii) the polymer wherein the repeating units (**Arg**-Gly-**Asp**) are separated by at least five neutral amino acids, as applied to the application claims 152 and 153; and (iii) the polymer wherein the repeating units (**Arg**-Gly-**Asp**) are separated by 54 amino acid residues, as applied to the application claims 155-157.

Claim Rejections - 35 USC §103

Claims 1-19 and 147-163 are rejected under 35 U.S.C. 103(a) as being obvious over Ferrari, F. A. *et al.* (US Pat. No. 5514581, newly cited) taken with Basu, S. *et al.* (*Biorg. Chem.* (1997) 8, 481-488).

Ferrari *et al.* disclose a polymer (SEQ ID NO: 102, columns 127-128) that is less than 50 KDa and comprises two repeating motifs, each of which contains a positively charged and a negatively charged moiety (**Arg**-Gly-**Asp**) wherein the two repeating units are separated by a neutral sequence having a distance larger than 32 Å (in view of that a dimension occupied by 8 amino acid residues is equivalent to 32 Å). The above Ferrari's disclosure teaches the all the limitations in regard to the polymer set forth in claim 1.

Claim 1 recites "a pharmaceutical composition"; note that the recitation of "pharmaceutical" has no patentable weight *per se*, absent factual indicia to the contrary; thus, the Ferrari's patent is applicable to the claim 1 disclosure. The Ferrari's patent teaches the subject composition for interacting with solution (see column 2, line 34) or combined with organic material (see column 48, line 10) which meets the limitation "pharmaceutical carrier" in the claim. Thus, Ferrari's teaching anticipates claims 1, 19 and 163 of the current application. Since the repeating unit is identical, Ferrari's patent also anticipates the application claims 3, 4 and

148. Because the repeating unit Arg-Gly-Asp has positive to negative charge ratio of 1:1, the Ferrari's patent is also applied to the application claims 18 and 162.

Ferrari *et al.* teach a polymer (SEQ ID NO: 111, columns 133-134) comprising non-repeating units wherein contain a positively and a negatively charged residues (see **Lys**-Gly-Ala-**Asp**, and **Arg**-Gly-**Asp**), as applied to claims 2, 5 and 147 of the instant application.

Ferrari *et al.* teach a composition produced by crosslinking the polymer with other type of polymer or materials, as applied to claims 6, 16 and 160 of the instant application.

Ferrari, *et al.* teach that the polymer is recombinantly synthesized (see abstract), as applied to the application claims 14-15 and 158-159.

Ferrari *et al.* disclose (i) a polymer (SEQ ID NO: 66, columns 101-104) that is less than 50 KDa and comprises five repeating motifs, each of which contains positively charged and negatively charged moieties, *e.g.*, the repeating unit I (**Lys**-Gly-**Asp**) and unit II (**Arg**-Gly-**Asp**) wherein the two repeating units I and II are contiguous, as applied to the application claim 154; (ii) the polymer wherein the repeating units (**Arg**-Gly-**Asp**) are separated by at least five neutral amino acids, as applied to the application claims 152 and 153; and (iii) the polymer wherein the repeating units (**Arg**-Gly-**Asp**) are separated by 54 amino acid residues, as applied to the application claims 155-157.

In addition, Ferrari, *et al.* teach (i) that the polymers which are characterized by having a small repeating sequence which provides for strands capable of associating, resulting in useful structural characteristics, where the strands are joined by turns or loops which are flexible and available for interaction with the environment (see abstract), and (ii) a polymer molecule having

14 of the characteristic repeating unit (**Arg**-Gly-**Asp**) (see SEQ ID NO:36, columns 67-74), as applied to claims 8-10 and 149-151 of the instant application.

Further, Ferrari, *et al.* teach a proteinaceous polymer comprising both the repeating unit and the intervening sequence for interacting with the environment, such as solutions, gases, gels and the like where the intervening sequence is substantially free of steric inhibition to interact with other molecules (see "summary of the invention" column 2, and claim 1), as applied to claims 11-13 of the instant application.

Yet, Ferrari, *et al.* does not expressly teach the modification of the polymer.

Basu *et al.* teach modification of the peptide polymer by conjugation with PNA (peptide nucleic acid), as applied to claim 7, and substituted cysteine with *D*-configuration cysteine in the polymer (see pages 482-483), as applied to claims 17 and 161 of the instant application.

It would have been obvious to one of ordinary skill in the art at the time the invention was made would have combined the teachings of the above references because the Ferrari *et al.* patent teaches Arg-Gly-Asp (RGD) repeating motif-containing polymer which meets all limitations of the current disclosure including the aspects regarding number of the repeating units and the dimension except the polymer modification, and because Basu *et al.* expressly teach the modified polymer that can form multimers (*e.g.*, PNA-DNA duplexes which comprises the spacer sequence, see page 485), which possesses the advantages for tissue-specific application in *vivo* (see abstract and also the following statement).

Further, when combined, one of ordinary skill in the art would have been motivated by: (**1**) Basu *et al.* explicitly teach *a*) the modified polymer, *e.g.*, introducing disulfide linkage(s) in the polymer, which would improve flexibility and favoring a bioactive conformation; *b*) *D*-Cys

modification that would increase biological stability against cellular proteases when *in vivo* applied (see the fourth paragraph at the left column, page 482); and *c*) the *D*-peptide-polymer (*i.e.*, mixed polymer) that would enhance cellular uptake, which is critical for *in vivo* application of the polymer (see abstract); and (**2**) the Ferrari *et al.* teaching offers an obvious advantages as to *a*) that the polymers are characterized by having small repeating units capable of associating, resulting in useful structural characteristics, where the functional units are joined by turns or loops which are flexible and available for interaction with the environment (see abstract); and *b*) the disclosed polymers provide a variety of favorableness of greater flexibility in controlling polymer biochemical and physical (*e.g.*, mechanical) properties, possess compatible functions, and produce unique chemical and physical properties due to interactions between the different repeating units (see lines 12-18, columns 8).

Thus, it would have been obvious to the skilled artisan to combine the above reference teachings to manipulate dimension between the functional repeating units (sequences) as well as number of the repeating sequences required for achieving desirable outcome, and arrive at the disclosed invention.

Given the above motivation one of ordinary skill in the art would have combined the teachings of the above references to produce the composition comprising the polymers characterized as the repeating charged motifs and spacer sequence(s) for modulating cellular events including immune response. Therefore, the claimed invention was *prima facie* obvious to make and use the invention at the time it was made.

Response to the rejection under 35 USC 103(a)

The response filed 4 November 2002 asserts that the Simmons reference teaches the polymer, *i.e.*, PNA-peptide that is less than 50 KDa, but the reference does not disclose that the polymer has at least two repeating charge motifs. Note that polynucleotide moiety of the polymer can form *duplexes* which is known from the prior art (see page 485 of Basu *et al.* reference). In virtue of this regard, the Simmons reference teach at least two repeating charge motifs. Therefore, the applicants' argument is not persuasive.

Also, the response asserts that neither Basu nor Nielsen adds anything to Simmons to render obvious the subject matter of claims 1, 6 and 7. Claims 6 and 7 are directed to the "mixed polymer" and "peptide-nucleic acid", respectively. Simmons' reference does not expressly teach either the mixed polymer or peptide-nucleic acid. Yet, Basu *et al.* teaches chimeric molecule, PNA-peptide polymer (PNA: peptide nucleic acid), while Nielsen specifically teach PNA polymer. Thus, the argument is not persuasive.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is (703) 306-3483.

The examiner can normally be reached from 9:00 a.m. to 5:00 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Christopher Low, can be reached on 703 308-2923. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this

application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

SWL

SWL

January 27, 2003

Christopher S. F. Low

CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600